

## **Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH  
Office of Tissues and Advanced Therapies**

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**NDA/BLA #s:** 125643  
**Products:** YESCARTA (axicabtagene ciloleucel), suspension for intravenous infusion  
**APPLICANT:** Kite Pharma  
**FROM:** Wilson W. Bryan, MD; Director, Office of Tissues and Advanced Therapies  
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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultation between the Office of Tissues and Advanced Therapies and the Office of Biostatistics and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASU) is necessary for YESCARTA (axicabtagene ciloleucel) to ensure that the benefits of the drug outweigh the risks of cytokine release syndrome (CRS) and neurologic toxicities. During the review of this application, FDA determined that the Applicant's proposed REMS, which consisted of a communication plan for healthcare providers, was not adequate to mitigate these risks. Over 90% of patients developed CRS during the pre-market evaluation of this product, and four CRS-related deaths were noted. Furthermore, many required intensive-care level facilities and the specific use of the monoclonal antibody tocilizumab to manage this adverse event. Additionally, over 80% of all patients experienced neurologic toxicities with the majority occurring during the CRS. One fatal neurotoxicity event from rapidly progressing cerebral edema was noted.

Due to the severe adverse events of CRS and neurotoxicity, which will both be included in a boxed warning on the Prescribing Information (PI), ETASU B and ETASU C will be required to ensure that the drug's benefits outweigh the risks. The REMS for YESCARTA (axicabtagene ciloleucel) requires that hospitals and their associated clinics that dispense YESCARTA are specially certified and have on-site, immediate (within 2 hours) access to tocilizumab. Furthermore, the REMS requires that as part of certification, those who prescribe, dispense, or

administer YESCARTA (axicabtagene ciloleucel) are trained about the management of CRS and neurotoxicity according to the YESCARTA Adverse Management Reaction Guide that is part of the YESCARTA REMS Program Live Training for Hospitals. YESCARTA (axicabtagene ciloleucel) will be dispensed only in certified hospitals and their associated clinics. The certified hospitals and their associated clinics will be required to put processes and procedures in place to ensure that healthcare providers who prescribe YESCARTA review the YESCARTA Prescribing Information and are aware of the patient monitoring instructions in the YESCARTA Prescribing Information. Hospital certification will also entail providing patients with information on CRS and neurotoxicity and informing them of the importance of staying within 2 hours of the certified hospital where they received YESCARTA for approximately 4 weeks after receiving YESCARTA treatment, unless otherwise indicated by their doctor, so that they can return to the treatment site for the treatment of CRS or neurotoxicity, if needed.

In reaching this determination, we considered the following:

- A. YESCARTA (axicabtagene ciloleucel), a CD19-directed, genetically modified autologous T cell immunotherapy, will be licensed to treat adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma. Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) estimated 72,580 new cases of Non-Hodgkin Lymphoma (NHL) and 20,150 deaths due to NHL in the United States in 2016. Diffuse large B-cell lymphoma (DLBCL) accounted for 30-40% of NHL cases. The current standard of care for the first-line treatment for large B-cell lymphoma is a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone in combination with an anti-CD20 monoclonal antibody (mAb) rituximab (R-CHOP). Second-line treatment also includes chemotherapy with Autologous Stem Cell Transplantation (ASCT) in patients with chemo-sensitive disease. However, 10-15% of treated patients exhibit primary refractory disease, and an additional 20-30% relapse<sup>1</sup>.
- B. Prognosis for these patients is poor, with an estimated 10% achieving long-term survival after ASCT<sup>2</sup> and the overall response rate (ORR) of 26%, complete remission (CR) rate of 7%, and the median overall survival (OS) of 6.3 months, in patients with r/r large B-cell lymphomas.
- C. The pre-specified primary endpoint for the pivotal licensure trial was overall remission rate (ORR) during the 6 months following YESCARTA (axicabtagene ciloleucel) administration. In the pivotal study, ZUMA-1, a total of 108 subjects were enrolled and treated with YESCARTA (axicabtagene ciloleucel). Of the 101 subjects whose data were evaluable for efficacy, the ORR (95% CI) was 72% (62, 81), with CR of 52% (41-62) and partial response (PR) of 21% (13, 30). The median duration of response (DOR) was 9.2 months and median follow up for DOR was 7.9 months. Efficacy was established on the basis of complete remission (CR) rate and duration of response (DOR), as determined by an independent review committee. These results demonstrate substantial efficacy of YESCARTA over available therapy in this disease population.

- D. Patients who have relapsed or refractory large B-cell lymphoma (see A above for subtypes) will be treated with this therapy within certain hospitals and their associated clinics which are accredited by the Foundation for the Accreditation of Cellular Therapy (FACT). Patients will undergo an apheresis procedure to obtain peripheral blood mononuclear cells. These cells will be (b) (4) and will be sent to a Kite Pharma manufacturing facility, where a retroviral vector is used to encode chimeric antigen receptor T cells. The cells will be shipped back to the treating hospital. Patients will receive lymphodepletion chemotherapy, and will then get a single intravenous dose of YESCARTA (axicabtagene ciloleucel) derived from their T cells. The target dose is  $2 \times 10^6$  CAR-positive viable T cells per kg body weight, with a maximum of  $2 \times 10^8$  CAR-positive viable T cells.
- E. Patients with large B-cell lymphoma do not have a baseline incidence of cytokine release syndrome. Neurologic toxicities that were observed with the product as detailed below, were not associated with large B-cell lymphoma or prior therapies. In the ZUMA-1 study, of the 108 subjects whose data were evaluable for safety, 94% (101/108) of subjects treated with YESCARTA (axicabtagene ciloleucel) experienced CRS and 13% had Grade  $\geq 3$  CRS (modified Lee criteria 2014) that included four fatal CRS events. CRS results in a constellation of inflammatory symptoms ranging from a flu-like syndrome to severe multi-organ system failure and death. Specifically, Grade  $\geq 3$  CRS requires treatment in an intensive care unit (ICU) setting with broad spectrum antibiotics, oxygenation supplementation and/or mechanical ventilation, and multiple vasopressors along with tocilizumab. In the clinical trial, CRS generally developed within the first 12 days after infusion with YESCARTA (axicabtagene ciloleucel) and the median CRS duration was seven days. Additionally, 85% (92/108) of subjects experienced neurotoxicity within 8 weeks of YESCARTA infusion, with 31% experiencing Grade  $\geq 3$  toxicity. The most common neurotoxicity events included encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia and anxiety. Serious or fatal events including cerebral edema, leukoencephalopathy and seizures were reported with YESCARTA. Neurotoxicity events developed within the first 43 days, and the median duration was 17 days. Almost all Grade  $\geq 2$  neurotoxicity events, which necessitate treatment with steroids, occurred during the first seven days post-infusion. Neurologic toxicities occurred during CRS or after CRS resolution and had longer time to resolution as compared to CRS. Few neurologic toxicity events occurred in subjects who did not experience CRS. In addition to the boxed warning for CRS and neurologic toxicity, the PI will contain the following adverse reactions within Warnings and Precautions: hypersensitivity reactions, serious infections, prolonged cytopenia, hypogammaglobinemia, secondary malignancies and impaired ability to drive and operate machinery.
- F. YESCARTA (axicabtagene ciloleucel) was given a breakthrough designation in the IND phase. YESCARTA is the second product in class CD19-directed genetically-modified autologous T-cell immunotherapy. YESCARTA is not a New Molecular Entity (NME).

The REMS will consist of elements to assure safe use, including that hospitals and their associated clinics that dispense YESCARTA must be specially certified and YESCARTA must be dispensed to patients only in specifically certified hospitals and their associated clinics, with an implementation system, and a timetable for submission of assessments of the REMS.

## References

1. Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K, McMillan A, Davies A, Stern S, Peggs K; British Committee for Standards in Haematology. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol*. 2016 Jul;174(1):43-56
2. Friedberg J: Relapsed/refractory diffuse large B-cell lymphoma. *Hematology Am Soc Hematol Educ Program*. 2011;2011:498-505.